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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,163	09/26/2006	Kenichi Koyakumaru	701062	7239

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EXAMINER
CLARK, SARA E

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,163	KOYAKUMARU ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 3/15/2010.

Claims 1 and 7 have been amended.

No new claims have been added.

Thus, claims 1-24 now represent all claims currently pending and under consideration.

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/19/2010 has been entered.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted.

WITHDRAWN REJECTIONS

Rejections under 35 USC §112

Due to the amendments to the claims, the rejection of claims 1-24 under 35 USC 112, second paragraph, for indefiniteness, is withdrawn.

Due to the amendments to the claims, the rejection of claims 1-24 under 35 USC 112, first paragraph, for lack of written description, is withdrawn.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Action dated 12/14/2009, on the ground that the references cited therein continue to read on the limitations of the amended claims.

Rejections under 35 USC §103

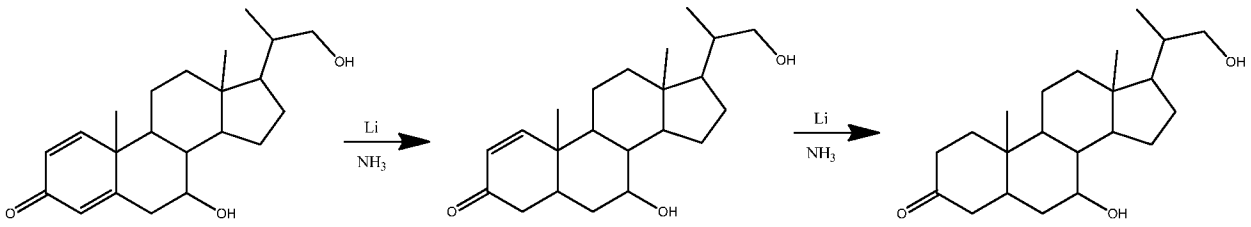
Claims 1-24 stand rejected under 35 USC 103(a) as obvious over Nakazawa and Moriarty.

RESPONSE TO ARGUMENTS

Applicant's arguments filed 3/15/2010 have been fully considered but they are not persuasive. Specifically, Applicant contends that the claims are directed to producing a mixture of compounds (II) and (III) (claims 1-6 and 13-18) or of compounds (VI) and (VII) (claims 7-12 and 19-24), which is directly related to the amount of the reducing reagent used in the reaction, and not ultimately obtained in the reaction of Nakazawa (Remarks, pp. 10-11). Applicant further contends that the selective partial reduction of the Δ1 double bond, resulting in the claimed mixtures, is not predictable, and thus is not inherently disclosed by Nakazawa (Remarks, p. 13). Finally, Applicant

contends that the claims recite an amount of reducing agent that is decreased from the conventional amount, such as the amount taught by Nakazawa (para. 0050).

While the final product of Nakazawa is 7,21-dihydroxy-20-methyl-pregna-3-one (claimed compounds (II), (IV), and (VI), rather than a mixture of 7,21-dihydroxy-20-methyl-pregna-3-one and 7,21-dihydroxy-20-methyl-pregna-1-ene-3-one (claimed compounds (III), (V), and (VII), as recited by the instant claims, the pregn-1-ene is inherently produced in the reaction as an intermediate (as shown below), because Nakazawa discloses the reaction using the same reagents in an amount which overlaps the range of claimed amounts.



As is well known, chemical reactions do not occur instantaneously; some amount of reactants, intermediates, and products are present in the reaction mixture as the reaction proceeds to completion. As the Applicants have shown, the Δ^4 double bond is more susceptible to reduction than the Δ^1 double bond. Thus, the pregn-1-ene inherently forms as an intermediate as the reaction proceeds. As the pregnane product begins to form, some amount of the pregn-1-ene will still be present in the reaction mixture. Thus, it is inherent in the reaction of Nakazawa that the claimed mixture of the pregn-1-ene and the pregnane is present*, even if only transiently, and even if this fact*

was not predictable or known. Inherency does not depend on predictability. A feature of a given process is inherently present every time it is carried out, or it is not.

The amount of reagent disclosed by Nakazawa does not alter the fact that the claimed compound mixture is inherently formed during the course of the reaction. The claims recite reacting compound (I) (the pregna-1,4-diene) with a metal catalyst (lithium) in an amount ranging from 1.6 to 5 molar equivalents relative to compound (I). Nakazawa discloses an amount of metal catalyst (lithium) ranging from 2 to 20 molar equivalents relative to compound (I).

As recognized by MPEP §2144.05, where claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In addition, Applicant cites Bansal 1996 (Remarks, p. 8), as evidence that it is well-known in the art that the theoretically required amount of metal (electron source) in a Birch reduction is two molar equivalents per one carbon-carbon double bond. Thus, the skilled artisan would have inferred that 4 molar equivalents of metal would be required to reduce the two double bonds of compound (I), or 3 molar equivalents to reduce every Δ4 double bond in the reaction mixture and half of the Δ1 double bonds, to yield the claimed compound mixture. These amounts lie inside both the claimed range and that disclosed by Nakazawa.

Therefore, it is immaterial that the claimed mixture of compounds is not the ultimate or final product of Nakazawa, or that the reference does not recognize that the Δ4 double bond is more susceptible to reduction than the Δ1 double bond, because

these are inherent features of the process disclosed by Nakazawa. As recognized by MPEP §2112, “the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer."

Nakazawa et al. disclose the claimed process using the 7,21-unprotected species of the claimed compounds; protection of the 21-hydroxyl group *following* the reduction reaction (para. 22); and TBDMS as a suitable hydroxyl-protecting group (para. 0042).

The only feature of the claimed invention Nakazawa does not disclose is protection of the 21-hydroxyl group *preceding* the reduction reaction, followed by deprotection.

Moriarty discloses protection of a 21-hydroxyl group with TBDMS preceding a Birch reduction reaction with lithium in liquid ammonia. Moriarty is cited as evidence that a skilled artisan would have a reasonable expectation that the claimed reaction would run in the presence of a TBDMS 21-hydroxyl-protecting group, regardless of the reasons contemplated by Moriarty for introducing it. Applicant admits on the record that one of ordinary skill in the art would understand that a Birch reduction could proceed in the presence of a TBDMS protecting group (Remarks, p. 14).

Nonetheless, Applicant contends that the obviousness rejection is overcome by evidence of unexpected properties, namely, that protection of the 21-hydroxyl group suppresses a side reaction, decreases the amount of reducing agent required, and allows the reaction to be controlled (Remarks, p. 14). However, the fact that applicant

has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Finally, Applicant contends that the obviousness rejection is overcome by evidence of unexpected results, namely, that the Birch reduction of the unprotected pregna-1,4-diene disclosed by Nakazawa results in a yield of 65% (Example 1, para. 105), while reduction of the claimed 21-hydroxy-protected pregna-1,4-diene results in a combined yield of 89% (76% of the pregnane plus 13% of the pregn-1-ene; Example 1). Adjusting these yields to account for the deprotection step (Example 2), the claimed process results in a final yield of 76% x 96% = 73% for the pregnane and 13% x 95% = 12.4% for the pregn-1-ene. Limiting the comparison to the yield of the unsaturated pregnane only, the claimed process increases the yield by only 8% (65% vs. 73%). Furthermore, while the specification discusses the principle of protecting the 21-hydroxy group in general (p. 3, line 23 to p. 4, line 3), there is no example directly comparing the identical process under identical conditions, wherein one starting material has a protected 21-hydroxyl group and the other has an unprotected 21-hydroxyl group.

Finally, evidence of unexpected results must be commensurate with the scope of the claims. As recognized by MPEP §716.02(d),

> Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980).

Because claims 1, 2, 5-8, and 11-24 recite any hydroxyl-protecting group, claims 1-4 and 7-10 recite any alkali or alkaline earth metal, and claims 1-24 recite any proton donor, it would be unreasonable to conclude that the data presented in Examples 1 and 2 supports a finding of unexpected results commensurate with the scope of the claims sufficient to overcome the *prima facie* case of obviousness. For these reasons, the rejection under 35 USC 103 of claims 1-24 is maintained.

NEW REJECTIONS

Claim Rejections - 35 USC § 112, First Paragraph

Written Description - New Matter

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

Specifically, claims 1 and 7 recite a metal "present in an amount of 1.6 to 5 molar equivalents" relative to the compound of formula (I). The disclosure, arguments, and supporting documentation (Bansal, 1996) do not provide adequate support for this limitation, which relate to the theoretically required amount of metal (electron source)

required to reduce a carbon-carbon double bond, rather than the actual amount required in practice, which can vary substantially from the theoretical amount required. For example, USPN 7,008,940 teaches that a Birch reduction with an alkali metal in liquid ammonia is carried out with about 1 to about 20 (molar) equivalents, preferably about 1 to about 5 (molar) equivalents of the alkali metal, such as sodium or lithium (col. 34, lines 32-58).

In addition, the specification discloses that the amount of the alkali metal to be used "is not particularly limited as long as the reduction of the carbon-carbon double bond at the 4,5-positions of compound (I) is almost completed and the carbon-carbon double bond at the 1,2-positions of compound (I) can partly remain. However, in order to significantly suppress the reduction of the ketone, the amount is generally within the range of 0.8 to 2.5 times the amount necessary for reducing the carbon-carbon double bond *at the 4,5-positions of compound (I)*" (specification p. 14, line 31 to p. 15, line 5; emphasis added), which amount is not disclosed with any specificity in the specification, original claims, or supporting documentation.

As recognized by MPEP §706.03(o), "[n]ew matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method." See MPEP § 608.04 to § 608.04(c).

CONCLUSION

Claims 1-24 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612